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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/578,453	05/26/2000	Jacques Mallet	03804.0114-02	9203

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EXAMINER	
SHUKLA, RAM R	
ART UNIT	**PAPER NUMBER**
1632	18

DATE MAILED: 11/19/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/578,453	MALLET ET AL.	
	Examiner	Art Unit	
	Ram R. Shukla	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-31* is/are pending in the application.

4a) Of the above claim(s) *27-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicants' response and amendments filed 8-9-02 have been received.

2. In view of the decision on applicants petition regarding restriction, the inventions of groups I-III have been joined.

3. Claims 27-31 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 10.

4. Claims 16-26 are under consideration.

5. The 112 second paragraph rejection is withdrawn in view of the joining of groups I-III.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 16, 17, 19, 20, 21, 22, 25, and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Michalovitz et al (Cell 62: 671-680, 1990) in view of Moberg et al (Journal of Cellular Biochemistry 49:208-215, 1992) and La Gal La Salle (Science 259: 988-990, 1993) for reasons of record set forth in the previous office action of 4-11-02.

Response to Arguments

Applicant's arguments filed 8-9-02 have been fully considered but they are not persuasive. Applicants have cited Promold and Tool Co. v. Great Lakes Plastics Inc., In re Dembiczak, and In re Gordon in support of their argument that there must be some teaching, suggestion, and or motivation in the prior art to lead one

of ordinary skill in the art ot modify or combine the teachings of the references. However, applicants have only cited parts of these case laws. For example, *Pro-Mold Tool Co. v. Great Lakes Plastics Inc.* 75 F.3d 1568, 1573, 37 USPQ2d 1626,1629 (Fed. Cir 1996) states:

"We note that: reason, suggestion, or motivation to combine two or more prior art references in single invention may come from references themselves, from knowledge of those skilled in art that certain references or disclosures in references are known to be of interest in particular field, or from nature of problem to be solved..."

Therefore, the reason, suggestion or motivation to combine references can come from knowledge of skilled in the art known to be of interest in particular field and in the instant case the knowledge that a p53 mutant suppresses transformation of wild type p53 is present in Michalovitz et al and provides motivation to use p53 mutant for inhibiting expression of wild type p53. Likewise, Moberg et al teaches that co-transfection of c-myc promoter construct with expression vectors expressing wild type or mutant p53. Applicants' arguments that the teachings of these arts do not teach motivation to provide mutant and wildtype p53 in adenoviral vectors are not persuasive because motivation to make an adenoviral vector one has to look at La Gal Salle, which teaches to use adenoviral vectors for transferring gene in brain both in vitro and in vivo. Next applicants argue that at best the office action implies that it might be obvious to try and that a clear and reiterate the requirement for combining specific teachings, in response it is reiterated that the motivation is provided by the arts used, as discussed above. Next, applicants argue that the office used hindsight and that the La Gal Salle reference does not provide motivation to specifically select adenoviral vectors. In response, it is noted that the point that the reference of La Gal Salle teaches to use an adenoviral vector for expressing a gene in neuronal cells over herpes simplex virus and it does not matter what is the advantage or disadvantage of any other vectors. Applicants' arguments that an artisan might have chosen other viral or non-viral vectors are misplaced since La Gal Salle is presenting the benefit of adenoviral vector compared to Herpes virus vectors (that are commonly used for

neuronal or glial cell specific gene expression but have poor infectivity and are pathogenic). The cited art teaches that adenoviral vector is better over herpes virus vector and that is a motivation to use adenoviral vector. Regarding applicants arguments that the cited art does not teach all the limitations of claims 22, 25 and 26, it is noted that the cited arts teach all the steps of the cited methods-administering a nucleic acid to cells and therefore, applicants arguments are not persuasive. It is noted that this is obviousness type rejection not a 102 rejection. In summary, the rejection of the claimed invention is maintained for reasons of record.

8. Claims 16-20, 22, 23, 25, 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Levrero et al. taken with Michalovitz et al. and Funk et al., and further in view of Chopp et al.

Levrero et al. (Gene, 1991) disclose a recombinant virus, specifically, a defective adenovirus for the purpose of harboring foreign nucleic acids in vitro and in vivo. The recombinant virus taught by Levrero et al. differs from the claimed recombinant virus in that the nucleic acids inserted into the recombinant adenovirus consist of the hepatitis B (HB) virus *s* gene or the CAT (chloramphenicol acetyltransferase) gene rather than nucleic acids from the group consisting of (a) nucleic acids encoding mutated p53 antagonists; (b) a p53 DNA binding site; and (c) nucleic acids encoding antisense RNA which inhibits p53 expression.

However, at the time the claimed invention was made, Michalovitz et al. (Journal of Cellular Biochemistry, 1991) disclosed mutated forms of various mouse p53 DNA clones (see Fig. 1, page 23) and reveals the ability of a mutant p53 to interfere with the function of *wt* p53 (page 25, column 2, 2nd paragraph). Funk et al. (Molecular and Cellular Biology, 1992) disclosed a specific DNA binding site for p53 identical to that of Sequence ID No. 2 (page 2866, abstract). The application of these nucleic acids to p53 expression is relevant due to the association of p53 with severe ischemic cell damage disclosed by Chopp et al. (Biochemical and Biophysical Research Communications, 1992). Chopp et al. disclose data

suggesting that induction of p53 may play a role in promoting cell death (page 1207, last paragraph). Therefore, the use of nucleic acids as disclosed by Michalovitz et al. and Funk et al. would interfere or block p53 activity and thus suppress p53 expression in cells such as neurons found in ischemic tissue.

Accordingly, in view of the teachings of Michalovitz et al., Funk et al., and Chopp et al., it would have been obvious for one of ordinary skill in the art at the time the claimed invention was made, to modify the recombinant virus taught by Levrero et al. for the expected effect of suppressing p53 activity. Thus, Applicant's claimed invention as a whole, was clearly *prima facie* obvious in the absence of evidence to the contrary.

9. Claims 22-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith taken with Soussi et al., and further in view of Chopp et al.

Smith (US Patent 5,087,617) discloses a method of inhibiting p53 expression in vitro and in vivo by administering nucleic acids encoding nucleic acids capable of blocking the mRNA transcribed from the p53 gene (column 5, lines 33-37). Smith differs from the claimed method in that the p53 antisense oligonucleotide does not have an identical sequence to that disclosed in Sequence ID No. 1. Also, Smith differs from the claimed method in that the target cells are cancerous cells of the hemopoietic system rather than neuronal cells.

However, at the time the claimed invention was made, Soussi et al. (Nucleic Acids Research, 1988) disclose a sequence identical to that of Sequence ID No. 1. The application of this nucleic acid to p53 expression is relevant due to the association of p53 with severe ischemic neuronal cell damage disclosed by Chopp et al. (Biochemical and Biophysical Research Communications, 1992). Chopp et al. disclose data suggesting that induction of p53 may play a role in promoting neuronal cell death (page 1207, last paragraph). Therefore, the use of nucleic acid as disclosed by Soussi et al. would interfere or block p53 activity and thus suppress p53 expression in cells such as neurons found in ischemic tissue.

Accordingly, in view of the teachings of Soussi et al. and Chopp et al., it would have been obvious for one of ordinary skill in the art at the time the claimed invention was made, to modify the method of Smith by administering a p53 antisense oligonucleotide for the expected effect of suppressing p53 activity by inhibition. Thus, Applicant's claimed invention as a whole, was clearly *prima facie* obvious in the absence of evidence to the contrary.

10. No claim is allowed.

When amending claims, applicants are advised to submit a clean version of each amended claim (without underlining and bracketing) according to § 1.121(c). For instructions, Applicants are referred to http://www.uspto.gov/web/offices/dcom/olia/aipa/index.htm.

Applicants are also requested to submit a copy of all the pending/under consideration claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for this Group is (703) 308-4242. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the Tiffiany N. Tabb whose telephone number is (703) 605-1238.

Ram R. Shukla, Ph.D.